UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/582,950	07/07/00	PETTIT G	5368-US

HM22/0518

RICHARD R MYBECK
SUITE 10
8010 EAST MORGAN TRAIL
SCOTTSDALE AZ 85258

EXAMINER	
VOLLANO, J	
ART UNIT	**PAPER NUMBER**
1621	3

DATE MAILED: 05/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/582,950	Pettit et al
Examiner	**Art Unit**
Jean F. Vollano	1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-10 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-10 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Priority

1. Applicant's claim for domestic priority under 35 U.S.C. 119(e) of 60/071070, filed 1/9/1998 and 60/11531 filed 12/9/199 is acknowledged. However, the provisional application upon which priority is claimed must be cross referenced in the first sentence of the specification according to the MPEP. Applicant has not complied with this requirement and is asked to make the appropriate correction. Also for completeness would Applicant also state in the first sentence of the specification that the application is the national phase of PCT/US99/00419, filed 1/8/1999, now WO99/35150.

2. The examiner notes that there are two sets of claims at the end of the application. One set is the original claims filed in the PCT application (9 claims) and the second is the amended claims which contains 10 claims. The examiner assumes that since there are 10 claims listed in the filing papers that the second set is what is to be examined. The examiner has appropriately crossed out the first set of 9 claims to avoid confusion.

3. The specification is objected to for the following reasons

In the specification on page 7 there is a formula in the figure of $(R^1O)_2PN^2_2$. There seems to be an R missing from the formula ?

On page 8 there is a definition of X=Z (divavalent). Shouldnt that be (divalent) ? There is a list of counter ions at the bottom of page which includes Ca^{2+} etc. However, letters g-s are not ions they are neutral compounds and it is unclear how the Z can be pyridine or morpholine. If they are neutral they would be covalently attached to the oxygen.The only way they could be ionic is if they were a pyridinum ion or a morpholinum ion. Also it is unclear if the moieties in g-s are forming a monovalent or divalent ion since the size of some of the compounds is large. It is noted thay Applicant is claiming these complexes and it is important that it is clear from the specification what is being described.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation of "and trans combretastatin A-4 prodrugs". The claim is claiming the method of preparing a prodrug and in the first scenario there prodrug bind made is a mono or disodium phosphate salt. However in the trans case there is no reference to what prodrug is being made (e.g. ester, phosphate, phosphite, carboxylic acid) . It appears to also be a sodium phosphate salt but that is not stated nor is it clear if it is a sodium phosphate if the mono

or disodium phosphate salts are being prepared when the compound is in the trans configuration. Also there is no nomenclature that is found in an on-line search for the term trans combretastatin A-4 . Is the combretastatin A-4 only a cis isomer ? The claim is confusing as to the metes and bounds of what is being claimed.

It is also unclear how one starts with combretastatin A-4 which appears to be cis isomer and with the same identical process makes the cis and the trans derivative. Is applicant claiming to prepare a racemic mixture? The preamble seems to be stating one or the other and not a racemic mixture of both.

Claim 1 recites the limitation of " phosphate ester of combretastatin A-4 having protective groups thereupon". This is confusing as to whether the protective groups are on the combretastatin A-4 ring or the phosphate ester.

Claim 1 recites the limitation of "to yield combretastatin A-4 prodrug disodium phosphate, the combretastatin A-4 prodrug sodium phosphate, or a trans-isomer thereof as the ultimate product". The phrase is confusing as to whether one or two or all three are made and under what conditions each is made. Does one get a disodium or a monosodium or both salts with the cis isomer or sometimes one gets just the trans isomer. Also if the product is the product then the other steps would be intermediates and the term "ultimate" product is not necessary. The claim is written in a convoluted manner which is confusing as to the metes and bounds of what is being claimed. The claim should be rewritten to clearly and concisely point out the instant invention being claimed.

Claim 2 recites the limitation of phosphorylating agents which include a phosphite a amido phosphine and a silyl amidophosphine. However after the phosphite the is a "/" and carbontetrachloride. It is unclear if the phosphite agent must be in carbon tetrachloride if it is used or if it can be in any solvent. Is the "/" placed to mean such as or is it the only limitation of a solvent. The claim is confusing as to the metes and bounds of what is being claimed.

Claim 5 recites "X-combretastatin A-4 3'-O phosphate wherein the "X" is selected from". As written it appears that the X is on the combretastatin and not the phosphate. The nomenclature is confusing as written. Also the X does not need to be in quotation marks since there is only one X cited. The claim is also confusing as to what is the "ultimate" product. Originally the "ultimate" product in claim 1 was a sodium or disodium salt. Now an additional ultimate product has been added that can include other alternatives. It is also noted that there is some essentially steps missing from claims 5-7 since the ultimate product has been changed but there are no steps incorporated to make the change. For example it is unclear how using sodium methoxide can produce a quinine moiety?. Claims 6-7 have similar problems with "Y" and "Z" and the term ultimate product. The claims are for a process and it is confusing as to how all these variations are prepared. Are they made from an exchange of the sodium salt which is what claim 1 is preparing or does one use potassium methoxide for the potassium salt? There is no pyridine methoxide so does the product form from another pyridine reagent or is the pyridine salt formed by exchange with the sodium ? Claims 5-7 are also objected to as being improperly dependent since they are not further limiting claim 1.

Claim 8 recites the limitation of "synthesizing a trans-isomer of combretastatin A-4 prodrug comprising:" There is no limitation on what kind of prodrug is being made and therefore the claim is confusing as written as to the metes and bounds of what is being claimed. The trans isomer is being prepared exclusively. However the cis isomer is being used as a starting material. Is this correct? The intermediate formed seems to be the cis isomer and the final product is the trans. This is confusing in light of the first set of claims which prepares a seeming mixture.

Claim 8 line 4 recites " cooling the solution". There has been no solution mentioned and therefore this limitation lacks antecedent basis.

After adding the silane to the reaction mixture the solvent is separated from the admixed solution to form an extract. There is no mention that the solvent contains the product. Usually the solvent is just that the solvent and does not contain the product. However in the next step the solvent extract is dissolve in methanol and forms a second solution and in that solution there is the product. Also there is the recitation of "the solid" this lacks antecedent basis.

The claim is written in a confusing manner and should be rewritten clearly and concisely point out what applicant is claiming as the instant invention.

Claim 9 recites the limitation of "Combretastatin A-4 metal and ammonium phosphate prodrugs and trans combretastatin A-prodrugs". There is no ammonium in the list of X and therefore it is confusing as to what is being claimed. A simpler and clearer way of presenting the claim would be to number each compound as (I) and (II) and state "The compounds of formula (I) and (II) ..... wherein X is selected".

The claims are replete with 35 U.S.C. 112, paragraph 2 problems. Above are some examples of the problems. However the list is not exhaustive. Applicant is asked to review the claims and make appropriate corrections to remove all the problems.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Rathbone et al (WO92/16486).

When Rathbone et al discloses the compound of the combretastatin A4 phosphate potassium salt (example 2, page 11) the claim is fully anticipated.

8. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Pettit (US5561122).

When Pettit discloses the compound of the combretastatin A4 phosphate potassium salt or sodium salt (example 2, page 11) the claim is fully anticipated.

9. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Pettit et al (Anti Cancer Drug Design 1995).

When Pettit discloses the compound of the combretastatin A4 phosphate potassium salt or sodium salt (examples on page 104) the claim is fully anticipated.

10. Anti cancer drug design-1995 by Pettit teaches the preparation of the sodium salt of Combretastatin A-4 by using sodium methoxide. Pettit teaches the preparation of the phosphate acid by the use of a trichlorethyl phosphorochloridate and combretastatin A-4 followed by addition of glacial acetic acid. However the preparation of the sodium or potassium salt is by the exchange of the ammonium salt formed by column exchange for the sodium or potassium salt by cation column exchange. A similar process is used to make the sodium and potassium salt in US5561122. WO92/16486 uses di ter-butoxy (N, Ndiethylamido)phosphine for the phosphorylating agent followed by the formation of the acid using trifluoroacetic acid. However the potassium salt is prepared by the substitution of a formed ammonium salt with a potassium cation exchanger.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr J F Vollano whose telephone number is (703) 305-4483. The examiner can normally be reached on Monday to Thursday from 6:30 to 5:00 .

12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter , can be reached on (703)308-4532 . The official fax phone number for the

organization where this application or proceeding is assigned is (703)308-4556. It should be noted that the examiner cannot immediately work on a fax sent to this number.

13. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-1235.

Jean F. Vollano

Primary Examiner

Art Unit 1621

May 15, 2001